PCT/IPO4/024
RU-403

INTELLECTUAL PROPERTY INDIA

सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Provisional Specification*** *filed in connection with Application for Patent No.* ***818/Del/2003*** *dated* ***19th June 2003.***

Witness my hand this 10th day of September 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

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AGIK 31/545

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"SOLVATES OF 3-PROPENYL-3-CEPHEM COMPOUND"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. NEERA TEWARI

c. SHAILENDRA KUMAR SINGH

d. BISHWA PRAKASH RAI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

ORIGINAL

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We. YATENDRA KUMAR, NEERA TEWARI, SHAILENDRA KUMAR SINGH, BISHWA PRAKASH RAI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (YATENDRA KUMAR)

b. (NEERA TEWARI)

c. (SHAILENDRA KUMAR SINGH)

d. (BISHWA PRAKASH RAI)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
   a. Provisional Specification (3 copies)
   b. Drawings (3 copies)
   c. Priority document(s)
   d. Statement and Undertaking on FORM – 3
   e. Power of Authority (Not required)
   f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **19TH** day of **June, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

0818-DEL-03

19 JUN 2003

FORM 2

The Patents Act, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

SOLVATES OF 3-PROPENYL-3-CEPHEM COMPOUND

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Amide solvates of cefprozil, which is 7β[(D)-2-amino-2-(4-hydroxyphenyl) acetamido]-3-(Z)-1-propenyl]-ceph-3-em-4-carboxylic acid, are provided. Further, processes for preparing the amide solvates, and processes for converting them to cefprozil monohydrate are provided.

Cefprozil is a cephalosporin antibiotic for oral administration known from US Patent No. 4,520,334, and has a broad spectrum of antibacterial activity against both Gram positive and Gram-negative organisms. US 4,694,079 discloses a crystalline dimethylformamide solvate of cefprozil characterized by a specified X-Ray diffraction pattern and its conversion to cefprozil via lyophilization from an aqueous solution.

We have found that cefprozil forms good crystalline solvates with N-methylpyrrolidone and N,N-dimethylacetamide. These solvates are easily crystallized out from the reaction mixture, and their conversion to cefprozil requires very mild conditions yielding pure cefprozil. The solvates serve as useful intermediates for preparing cefprozil.

In one aspect, there is provided N-methylpyrrolidone solvate of cefprozil. In a second aspect, N,N-dimethylacetamide solvate of cefprozil is provided.

There is also provided a process preparing these solvates, which comprises adding N-methylpyrrolidone and N,N-dimethylacetamide to an aqueous solution of cefprozil at a pH of about 4.5 to about 6.5 and isolating the respective solvates.

Further, a process preparing crystalline cefprozil, which comprises stirring the N-methylpyrrolidone solvate or the N,N-dimethylacetamide solvate in an aqueous solvent at a temperature of about 20°C to about 60°C to obtain crystalline cefprozil, is also provided.

In general N-methylpyrrolidone solvate of cefprozil may be characterized by a crystalline structure containing cefprozil and N-methyl pyrrolidone in the molar ratio of 1: 1.5. N-methylpyrrolidone solvate of cefprozil may also be characterized by strong X-ray peaks at about 6.24, 6.48 and 18.64 degrees two-theta.

In general N,N-dimethylacetamide solvate of cefprozil may be characterized by a crystalline structure containing cefprozil and N,N-dimethylacetamide in the molar ratio of 2: 1.5. N,N-

dimethylacetamide solvate of cefprozil may also be characterized by strong X-ray peaks at about 6.48, 7.08, 8.46 and 18.78 degrees two-theta, and medium X-ray peaks at about 18.32, 20.06, 21.64, 22.16 and 24.7 degrees two-theta.

An aqueous solution of cefprozil used for preparing the solvates may be obtained directly from a reaction in which cefprozil is formed. It may also be obtained by dissolving a salt of cefprozil, or adding a base to a suspension of cefprozil in an aqueous solvent.

Examples of suitable bases include alkali metal salts of carboxylic acids, such as sodium acetate and potassium acetate; organic amines, such as triethylamine, pyridine, picoline, ethanolamine, triethanolamine, and dicyclohexylamine; ammonium hydroxide; alkali metal hydroxides, such as sodium hydroxide and potassium hydroxide; alkali metal carbonates, such as sodium carbonate and potassium carbonate; and alkali metal bicarbonates such as sodium bicarbonate.

The above bases may also be used for adjusting the pH of the aqueous solution of cefprozil to about 4.5 to about 6.5. For example, the pH may range from about 5.5 to about 6.5 in some particular embodiments.

While at least 1.5 moles of N-methylpyrrolidone, or 0.75 moles of N,N-dimethylacetamide need to be added per mole of cefprozil used, a substantial excess of N-methylpyrrolidone, or N,N-dimethylacetamide may be used. Volumes of N-methylpyrrolidone, or N,N-dimethylacetamide ranging from one to 10 times the volume of aqueous solution of cefprozil may be used. For example, three to six volumes of N-methylpyrrolidone, or N,N-dimethylacetamide may be used in some particular embodiments.

Aqueous solvents for preparing the solvates may be any water miscible organic solvents in admixture with water. Examples of suitable water miscible solvents include ketones such as acetone and ethylmethyl ketone; acetonitrile; alcohols, such as methanol, ethanol, propanol, and isopropanol; cyclic ethers, such as dioxane and tetrahydrofuran; and mixture(s) thereof. The cefprozil or its salts to be used in preparation of the solvates can be obtained by methods known in the art including those described in US 4520022, US 4727070, US 5608055, US 2002/120136, US 6060268, US 6333409, and pending Indian applications

1024/ DEL/ 2002, and 353/ DEL/ 2003 filed by the present inventors. The starting cefprozil may be obtained as an aqueous solution directly from a reaction in which cefprozil is formed, for example in the patents/ patent applications listed above, and used as such without isolation.

Generally, the solvate precipitates out of the solution or the reaction mixture spontaneously. The precipitation may also be facilitated by adding seeds of the solvate. The precipitation may also be induced by reducing the temperature.

The precipitated solvate may be isolated by conventional methods such as filtration or centrifugation, optionally followed by washing and/or drying.

The conversion of the solvates to crystalline cefprozil is performed at a temperature of about 20 °C to 60 °C and may range from about 35 °C to about 50 °C. For example the temperature may range from about 45 °C to about 50°C in some embodiments.

Aqueous solvents for conversion of the solvates to crystalline cefprozil may be the same as those described above for the preparation of the solvates.

The crystalline cefprozil product may be obtained as a monohydrate or a hemihydrate of cefprozil. Conversion of the solvates to crystalline cefprozil in the desired form may be facilitated by adding seeds of the desired form of crystalline cefprozil or by reducing the temperature.

The crystalline cefprozil obtained may be isolated by conventional methods such as filtration or centrifugation, optionally followed by washing and/or drying.

In the following section embodiments are described by way of examples to illustrate the process of invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

METHODS

Powder XRD

X-Ray Difractometer, Rigaku Coorperation,RU-H3R
Goniorneter CN2155A3
X-Ray tube with Cu target anode
Divergence slits 1 0 , Receiving slit 0.15mm, Scatter slit 1 0
Power:40 KV, 100 mA
Scanning speed: 2 deg/min step: 0.02 deg
Wave length: 1.5406 A

FT-IR

Instrument:Perkin Elmer,16 PC
SCAN: 16scans, 4.0 cm.-1
according to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

EXAMPLE – 1

Preparation of 7[(D)-2-amino-2-(4-hydroxyphenyl) acetamido]-3-(Z/E)-1-propenyl]-ceph-3-em-4-carboxylic acid (cefprozil), N,N-dimethylacetamide solvate (2:1.5)

Solution A - To a stirred slurry of 7 amino-3-[(Z/E)-1-propen-1-yl]-cephe-3-em-4-carboxylic acid (100 g) in methylene chloride (500ml) were added hexamethyldisilazane (50g), trimethylchlorosilane (35g) and imidazole(1.0g). Reaction mixture was refluxed for 4 hours and then cooled to -10 °C.

Solution B - Potassium (D)-N-[1-methoxycarbonyl propen-2-yl]- α-amino-p-hydroxyphenylacetate (dane salt, 141g) was stirred in methylene chloride (600ml). N,N - dimethylacetamide (DMAc, 400ml) was added and the slurry was stirred at -35 to - 40°C. N-methylmorpholine(0.8g) and ethylchloroformate(56.5g) were added, the mixture stirred for 1.5 hours at –35 to -40°C and then cooled to -65°C.

Above silylated mass (solution A) was added into mixed anhydride (solution B) at -65°C and stirred for 1 hour at –40 °C. The temperature was raised to -30 to -25°C and further stirred for 1.5 hours. A mixture of water (350 ml) and hydrochloric acid (35%, 75ml) was added to the reaction mixture and stirred for 15 minutes at 0 to 5°C. Aqueous layer was separated. Dimethylacetamide (1500ml) and acetone (300 ml) were added to the aqueous layer. pH of mixture was adjusted to 6.0 with ammonia solution (25%) and stirred for 2.0 hours at 20-25°C. The solid obtained was filtered and washed with dimethylacetamide (200ml) followed by acetone. After drying at 40°C, 150g of the title solvate was obtained.

Moisture content (by KF) =0.7% w/w

^{1}H-NMR (D2O-DCl), δ(ppm): 7.4 (d, 2H), 6.94 (d, 2H), 5.97(d, 1H), 5.71-5.78 (m, 1H), 5.66 (d, 1H), 5.0-5.13 (d, 2H), 3.29-3.48 (m, 2H), 3.20 (s, 2H), 2.91(s, 2H), 2.09 (s, 2H), 1.53-1.55 (d, 3H).

IR in KBr pellet (cm^{-1}) – 3422, 3217, 3025, 1764, 1697, 1558, 1518, 1400, 1349, 1263.

X-Ray powder Diffraction:

d-value (°A)	2θ (°)	I/Io %
13.63	6.48	100
12.47	7.08	87
10.44	8.46	73
10.15	8.70	64
6.65	13.30	30
6.32	14.00	30
4.84	18.32	54
4.72	18.78	93
4.42	20.06	57
4.29	20.70	48
4.17	21.28	47
4.10	21.64	62
4.01	22.16	53
3.91	22.72	43
3.60	24.70	42
3.42	26.00	40
3.35	26.58	38

EXAMPLE 2

Preparation of 7[(D)-2-amino-2-(4-hydroxyphenyl) acetamido]-3-(Z/E)-1-propenyl]-ceph-3-em-4-carboxylic acid (cefprozil), N-Methyl-2-pyrrolidone solvate (1:1.5)

7-APCA (50g) was reacted according to the procedure described in Example 1 using N-methyl-2-pyrrolidone instead of dimethylformamide to obtain 76g of the title solvate.

^{1}H-NMR (D2O-DCl), δ(ppm): 7.2-7.25(d, 2H), 6.80-6.83(d, 2H), 5.87-5.91 (d, 1H), 5.61-5.68(m, 1H), 5.54-5.55(d, 1H), 5.02-5.03(d, 2H), 3.12-3.34(m, 2H), 2.6-2.7(s, 3H), 2.29-2.35(t, 2H), 1.94-1.84(m, 2H), 1.42-1.45(d, 3H).
IR in KBr pellet (cm^{-1}) – 3420, 3216, 3028, 1779, 1699, 1667, 1567, 1518, 1448, 1400, 1350.

X-Ray powder Diffraction

d-value (°A)	2θ (°)	I/Io %
14.15	6.24	99
13.63	6.48	96
5.05	17.54	26
4.75	18.64	100
4.59	19.30	44
4.51	19.66	33
4.43	20.02	40
4.18	21.22	31
4.06	21.86	44
3.60	24.74	31
3.32	26.80	27

EXAMPLE 3

Preparation of Crystalline Cefprozil Monohydrate

Cefprozil dimethylacetamide solvate (100g) prepared in Example 2 was stirred in water (200ml) at 40-45°C for 120minutes. It was then cooled to 5-8°C and filtered to obtain crystalline cefprozil monohydrate.

Yield : 74.0g

Moisture content (by KF) =4.5% w/w

HPLC (Assay) – 100.1% on dry basis.

EXAMPLE 4

Preparation of Crystalline cefprozil monohydrate

Cefprozil N-methyl-2-pyrrolidone solvate (50g) as prepared in Example 3 was stirred in water (150ml) at 45-50°C for 120 minutes. The mixture was cooled to 0-5°C and crystalline cefprozil monohydrate was collected by filtration.

Yield : 35g

Moisture content (by KF) =4.8% w/w

HPLC (Assay) – 99.8% on dried basis.

Dated this **19TH** day of **JUNE, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)

Company Secretary

ABSTRACT

New amide solvates of cefprozil are provided. Process for preparing the solvates, and processes for converting them to cefprozil monohydrate are given.